UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,824	08/10/2001	William Gavin	10275-146001 / TCI-146	6238

31904 7590 05/17/2005

GTC BIOTHERAPEUTICS, INC.
175 CROSSING BOULEVARD, SUITE 410
FRAMINGHAM, MA 01702

EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,824	GAVIN ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,8,9,11,13,16-24 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,8,9,11,13,16-24 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-5, 8, 9, 10, 13, 16-26 and 33 as amended (2/23/2005) are pending and under examination.

Claim Rejections - 35 USC § 112

Indefinite

Claims 1, 3-5, 8, 9, 10, 13, 16-23 and 33 as amended remain/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Acknowledged amendments of claim 1, 13 and 24 in attempt to correct antecedent basis for "first", "second" and "third" structural elements including sample, solution, sampler solution, buffer, temperature, and time periods. Yet, with respect to claim 1, last amendment appears to result in introduction of new matter (see below). Claim 13 is rendered indefinite by insertion of newly amended step (d) that encompasses addition of glycerol to sperm because addition of glycerol is believed to be intended before freezing step but step (d) is recited after step (c) in the sequence of events from (a) to (e).

Claim 33 as amended now lacks antecedent basis for antibiotic(s) in claim 13 as amended. With respect to the instant claim 13 it is noted that it has been amended to exclude antibiotic. But the as-filed specification describes the use of antibiotics in both "first" and "second" solutions as intended for the cooling stage solution without glycerol and for the freezing stage solution with glycerol (page 3, lines 8-14 and lines 12-23).

New matter

Claims are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Insertion of the limitation drawn to second temperature "between - 40° C and - 100° C" to equilibrate glycerol and sperm and /or maintained sperm with glycerol for 4-21 hours at second temperature "between - 40° C and - 100° C" has no support in the as-filed specification.

The insertion of this limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limited genus that would show possession of the concept of the use of second temperature "between - 40° C and - 100° C" to equilibrate glycerol and sperm and /or maintained sperm with glycerol for 4-21 hours at second temperature "between - 40° C and - 100° C".

The as-filed specification describes that the second temperature "between - 40° C and - 100° C" is applied for 7-20 minutes (paragraph bridging page 3 and 4; original claims 10 and 11). The particular examples describes that the second temperature "- 80° C" is applied for 15-20 minutes (page 16, line 13; page 19, line 6). The as-filed specification describes that glycerol is added before freezing at temperature "between - 40° C and - 100° C" (specification page 3, lines 15-31). The equilibration period for sperm and glycerol (part B extender, see page 15 at line 5) happens before freezing at the temperature "- 80° C" (page 16, lines 4-13).

Thus, there is no sufficient support for the new genus drawn to equilibration between sperm and glycerol at temperature "between - 40° C and - 100° C" for 4-21 hours. This is a

matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertion of new limitation is considered to be the insertion of new matter for the above reasons.

Applicants are hereby notified that the insertion of new matter into the claims has necessitated the removal of some art rejection(s) over the instant claims. However, removal of new matter will result in the reinstatement of the art rejection(s).

Claim rejection under 35 U.S.C. 102(b) as anticipated by SU 986, 411 {Nauk et al.) or, in the alternative, under 35 U.S.C. 103(a) as obvious over SU 986, 411 (Nauk et al.) in view of US 3,940,943 (Sikes et al.) and Royere et al. has been withdrawn because SU describes rapid freezing in vapor of liquid nitrogen at - 120° C to - 160° C (see abstract or see table 2) for 8-8.5 minutes (see abstract or see translation page 5, lines 17-18) and because SU does not describe temperature such as "between - 40° C and - 100° C " to equilibrate glycerol and sperm and /or maintained sperm with glycerol for 4-21 hours as presently claimed. The cited US '943 (Sikes) teaches away from the use of glycerol in particular exemplified disclosure of the method for sperm preservation. The reference Roger et al. teaches general concepts of sperm slow cooling and rapid freezing without indicating particular temperature and time intervals.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-5, 8, 9, 10, 13, 16-26 and 33 as amended remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over SU 986, 411 (Nauk et al.) and US 3,940,943 (Sikes et al.) and Royere et al. and US 3,791,384 (Richter et al.) and Ahmad et al. as explained in the prior office action.

Claims are directed a method of preserving mammalian sperm and storing the sperm comprising step of slow cooling sperm to a first temperature between + 2° C and +10° C, step of rapid freezing sperm at/to second temperature of about - 40° C and - 100° C and step of storing sperm at - 190° C to - 200° C, wherein the cooling step comprises the use of a cryoprotectant buffer/solution/sample without glycerol, wherein glycerol is added before freezing step. The sperm is cooled and/or hold at cooling/freezing temperatures for either 4-21 hours or 7-20 minutes or 1.5-4 hours as claimed. The sperm is frozen at temperature - 40° C and - 100° C for about 7-20 minutes or 10-15 minutes. Some claims are further drawn to the use of cryoprotectant buffer comprising egg yolk at concentration of 10-30 %, antibiotics, sugar, Tris buffer and citric acid. Some claims are further drawn to a method of making an animal by fertilizing an oocyte with the preserved sperm. Some claims are further drawn to the use of specific antibiotics selected from tylosin, gentamicin, lincospectin and/or spectinomycin.

The cited references are relied upon as explained in the prior office action and repeated herein.

SU 986, 411 is relied upon as explained in the prior office action for the disclosure of a method for preservation of mammalian sperm by protocols encompassing slow cooling and rapid freezing of the sperm. Royere et al. and US 3,940,943 disclose the similar concepts of step-wise cooling and freezing of sperm. Royere et al. also teaches the concept of reducing possible toxic effects of glycerol by adding glycerol to the cooled sperm sample before freezing (page 556, col. 2, lines 8-10). Although US 3,940,943 does not teach the use of glycerol in the particular example, it has been relied upon for the teaching about 5-10% glycerol in common and standard cryopreservation solutions (col.1, lines 26-27).

The references SU 986 411, US 3,940,943 and Royere et al. are lacking particular disclosure about the use of specific antibiotics. However, the reference by Ahmad et al. demonstrates the use of antibiotics tylosin, lincospectin and gentamicin in the solutions together with egg-yolk-Tris components in the method for preserving mammalian sperm by stepwise sperm cooling and freezing (abstract and page 2440, col. 1, par. 2). The cited patent US 3,791,384 also teaches the use of other components in composition/solution for sperm preservation including Tris buffer, fructose, citric acid and antibiotics including streptomycin (col. 5, line 10-15; col. 2, lines 65-68 and col. 3, lines 1-5).

Therefore, it would have been obvious at the time the claimed invention was made to practice a mammalian sperm preservation method encompassing the use of slow cooling/rapid freezing of sperm and the addition of glycerol to the cooled sperm before freezing with a reasonably expectation in success for preserving the sperm intended for fertilization because substantially similar protocols have been taught and suggested in the prior art as adequately demonstrated by all cited references (SU 98641 1; US 3,940,943; Royere et a1.). One of skill in

the art would have been motivated to use typical cryoprotectant buffer formulations with egg yolks and glycerol for the expected benefits of sperm preservation intended for fertilization as demonstrated in the prior art (SU 98641 1; US 3,940,943; Royere et al.). One of skill in the art would have been motivated to add glycerol to the cooled sperm sample before freezing for the expected benefits in reducing possible toxic effects of glycerol on mammalian sperm (SU 98641 1; Royere et al.). It would have been obvious at the time the claimed invention was made to add antibiotics and/or other components including Tris buffer and citric acid the cryoprotectant compositions intended for sperm preservation since all presently claimed ingredients are known and have been used for sperm preservation as adequately demonstrated by the cited references US 3,791,384 and Ahmad et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicants' arguments filed 2/23/2005 have been fully considered but they are not found persuasive.

With regard to the teaching of SU (Nauk et al.) applicants argue (response page 11 and response page 14) that SU does not teach a specific sequence of treating, cooling and freezing sperm sample down to the temperature - 190° C to - 200° C and storing sperm at - 190° C to - 200° C. This is not particularly true because Nauk et al. discloses that after freezing in vapor of

liquid nitrogen the frozen sperm samples were lowered into liquid nitrogen (see translation page 5, line 18-19) and, thus, the frozen sperm was stored at about - 190° C to - 200° C temperature of liquid nitrogen. In alternative, even if the frozen sperm in the Nauk's method is stored at -140° C (-120° C to - 160° C; see table 2) but not clearly at - 190° C to - 200° C as claimed, the motility of sperm is preserved as disclosed by Nauk (table 2). Thus, the differences in effects of long term storage either in vapor of liquid nitrogen or in liquid nitrogen are not particularly clear as argued (response page 11, argument d).

Applicants appear to argue that Nauk's method provides for 5 temperature steps (response page 11, arguments a and b). Yet, the argued "extra" steps between room temperature and zero are inherently present in the claimed method because sperm is also cooled down from the body/room temperature to zero as claimed and because the cooling rates and total cooling times are the same as claimed (from 0.2° C/min to 0.5° C/min for 1.5-4 hours) and as disclosed by Nauk (table 1). It is also noted that the other cited reference by Ahmad et al. teaches that sperm sample is cooled down to 5° C in 2 hour from 35° C to 5° C and, thus, at rate 0.25° C/min (page 2440, col.1, par. 2) which is within the claimed range.

With regard to "glycerin equilibration" (page 11 argument c; page 12 argument h) it is noted that glycerol and sperm equilibration is done + 4° C as taught by Nauk and as claimed.

Applicants also argue that the Spermosan-3 in the method of Nauk is not a single antibiotic (page 11, argument e). However, the instant claim 33, drawn to antibiotic is written as Markush group, and, thus, antibiotic compound might be a mixture. Moreover, the cited Ahmad' reference teaches that the presently claimed "Lincospectin" is a not a single compound but contains lincomycin and spectinomycin (page 2439, col. 2, last par.).

Applicants argue (page 1, argument f; page 12, argument i) that sperm is maintained at first temperature for 4-21 hours. However, in the instant claim 1 "first" temperature is a freezing temperature and, thus, limitation about 4-21 hours has no support in as-filed specification as explained above. With respect to claims 13 and 23 it is noted that, although Nauk et al. teaches holding at + 4° C for about 3-3,5 hours, this prior art holding time that is about the same as the presently claimed "4 hours" (low limit of the range). Moreover, the "4 hours" claimed limitation is the applicants' preferred embodiment (instant specification page 3, line 21). Furthermore, the other reference by Ahmad et al. teaches holding sperm at "first" temperature + 5° C for 4 hours before freezing (page 2440, col. 1, par. 2) that is within the claimed range(s).

Applicants argue that claim 13 and 24 limitation drawn to freezing at "between - 60° C and - 90° " is not taught by Nauk and/or not suggested by other prior art references (page 12, argument g). However, claim 13 is not limited by time period for freezing at "between - 60° C and - 90° " and, thus, the method of Nauk et al. is the same with respect to this limitation because it teaches freezing in liquid nitrogen vapors (between - 120° C to - 140/160° C) after glycerol treatment at about zero temperature and, thus, the sperm sample is exposed to freezing temperature "between - 60° C and - 90° " for at least some period of time when the sperm sample is transferred from refrigerator to freezer and/or when temperature of the sperm sample drops from zero to - 120° C. Moreover, Nauk also discloses that freezing is conducted at - 80° C (see translation page 3, line 7). The reference by Roger also teaches freezing temperature ranges between - 40° C and - 80° C (page 557, col.1, line 3). With respect to the claim 23 limitation drawn to freezing sperm at "between - 60° C and - 90° " for "between 7 minutes and 20 minutes" and with respect to the claim 24 limitation drawn to freezing sperm at "between - 60° C and - 90°

" for "10 minutes to about 15 minutes" it is noted that Roger teaches commonly used time intervals of about 8-30 minutes for the freezing step (page 556, col. 2, last par.). Roger further concludes that various protocols of the sperm rapid freezing step before sperm storing in liquid nitrogen have about the same effects on sperm survival (page 557, col. 1, par. 1).

Therefore, the claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1651

May 13, 2005

V. Afremova

VERA AFREMOVA

PRIMARY EXAMINER